Atty Dkt. No.: 10971722-2
USSN: 09/802,358

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Signature	Donna Macedo	**Date**	2/4/02

AMENDMENT UNDER 37 C.F.R. §1.111 Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Application Number	09/802,358
	Confirmation Number	Unassigned
	Filing Date	March 9, 2001
	First Named Inventor	Ach et al.
	Examiner	A. Chakrabarti
	Group Art	1655
	Attorney Docket No.	10971722-2

Sir:

This amendment is responsive to the Office Action dated November 7, 2001 for which a three-month period for response was given making this response due on or before February 7, 2002. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

AMENDMENTS

IN THE SPECIFICATION

Please insert the following two paragraphs after the heading "INTRODUCTION" on page 1:

Cross-Reference to Related Applications

This application is a divisional of U.S. patent application serial no. 09/359,564, filed July 22, 1999.

Please replace the paragraph beginning on page 16, line 3 with the following rewritten paragraph:

The above steps of contacting the ribonucleic acid with the polymerase and labeled ribonucleotide result in the production of an end-labeled ribonucleic acid characterized by the presence of one or more labeled ribonucleotide residues sequentially attached to the 3'

terminus of the original ribonucleic acid via a phosphodiester linkage. The number of labeled ribonucleotide analogue residues that may be attached is at least 1, may be at least 2, where the number may be as high as 5 or 10 or higher.

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 17-23 are pending after entry of the amendments set forth herein.

Claims 17-20 were examined and were rejected, claims 21-23 having been withdrawn from consideration due to restriction.

The specification has been amended to insert a priority claim and to correct a typographical error.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Restriction Requirement

The Examiner has imposed a restriction requirement, requiring the election of the claims of either Group I, i.e., claims 17-20; or Group II, i.e., claims 21-23; for further prosecution in this application.

During a telephone conversation with Gordon Stewart on July 26, 2001, the Applicants made a provisional election with traverse to prosecute the invention of Group I, claims 17-20. The Applicants hereby affirm this election of Group I.

The Applicants also respectfully urge the Examiner to rejoin the claims of Group II with the elected claims of Group I for examination in this application for the following reasons.

The MPEP allows an Examiner to examine otherwise patentably distinct sets of claims if to do so would not impose an undue burden on the Examiner. M.P.E.P. § 8.03 states that:

> **If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.**

In the present case, the claims of Group I are directed to a kit for use in end-labeling ribonucleotides with non-radioactively labeled nucleotides. Specifically, the kit comprises a non-radioactively labeled ribonucleotide and a prokaryotic poly(A) polymerase. The claims of Group II are drawn to a method for detecting the presence of a target ribonucleic acid in a sample of a plurality of different ribonucleic acids, wherein the method includes end-labeling the nucleic acids of the plurality using non-radioactively labeled ribonucleotides and a prokaryotic poly(A) polymerase.

The Examiner has already fully searched the claims of Group I, i.e., a kit comprising a non-radioactively labeled ribonucleotide and a prokaryotic poly(A) polymerase. This search for the claims of Group I would also have found prior art relating to the claims of Group II, since the claims of Group II merely recite use of the components of the kit in a method for detecting the presence of a target ribonucleic acid, and a common use of the kit is in such methods.

The Applicants made the surprising discovery that *E. coli* poly(A) polymerase attaches non-radioactively labeled ribonucleotides to the 3' end of a ribonucleic acid. Once the Applicants showed that such attachment is possible, one of skill in the art would expect that other prokaryotic poly(A) polymerases would also attach non-radioactively labeled ribonucleotides to a ribonucleic acid because the prior art illustrates the behavioral similarity among prokaryotic poly(A) polymerases. For example, it is known that the two poly(A) polymerases identified in *Bacillus subtilis* resemble the two major poly(A) polymerases of *E. coli*, both with respect to both size and catalytic properties (*See, e.g.,* Sarkar et al., *Biochem. Mol. Biol. Int.* (1997) 41(5):1045-50 (copy enclosed)).

Furthermore, if one does a BLAST search of Genbank using the E. coli poly(A) polymerase protein sequence, one can find that the enzyme has significant regions of homology with other prokaryotic RNA polymerases, ranging from 91% identity to Salmonella poly(A) polymerase, on down to less extensive, but still substantial, homology with poly(A) polymerases from Yersinia pestis, Vibrio cholerae, and Xylella fastidiosa, among others. This conservation of sequence implies conservation of functionality, and thus conservation of the ability to add non-radioactively labeled nucleotides to RNA.

Accordingly, one of skill in the art would expect that prokaryotic poly(A) polymerases, other than *E. coli* poly(A) polymerases, would also work in the present invention because it is known that prokaryotic poly(A) polymerases act predictably in the same manner. As such, a demonstration that one prokaryotic poly(A) polymerase works according to the claimed invention gives one a reasonable expectation of success that other prokaryotic poly(A) polymerase work as well. Moreover, the Office has provided no reason to doubt that other prokaryotic poly(A) polymerases would also attach non-radioactively labeled ribonucleotides to the 3' end of a ribonucleic acid. The Applicants thus respectfully request withdrawal of this rejection of Claims 17-20 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §103(a)

Claims 17-20 have been rejected under 35 U.S.C. §103 over Life Technologies in view of Urdea, and further in view of Matthews et al. The Office Action asserts that it would

have been obvious to one of skill in the art to combine and substitute the non-radioactively labeled ribonucleotide of Urdea into the method of end-labeling ribonucleic acids with the labeled ribonucleotides and poly(A) polymerase of Life Technologies, and that Matthews et al. teaches the motivation to use fluorescent labels as alternatives to radioisotopic labels.

According to MPEP §2142, an examiner must meet three basic criteria to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. The combination of Life Technologies, Urdea, and Matthews et al. do not meet all three of these criteria.

Life Technologies is a catalog page describing an *E. coli* poly(A) polymerase and showing reaction conditions for use of the poly(A) polymerase to radioactively end-label ribonucleic acids. Urdea simply describes various types of fluorescent labels that have been used to label polynucleotides, while Matthews merely describes some problems encountered with the use of radioactive labels.

The combination of these three references would not have provided one of skill in the art with a reasonable expectation of success because, at the time the invention was made, it was known in the art that use of poly(A) polymerase to attach end-label ribonucleic acids with non-radioactive labels was problematic. For example, Rosemeyer et al. (U.S. Patent No. 5,573,913) states:

> The attachment of nucleotides to the 3' end of RNA molecules using...poly(A) polymerase does...have considerable problems.... The efficient labelling of 3' ends of RNA molecules with poly(A) polymerase is limited to the use of ATP and ATP derivatives since bases other than A are accepted much more poorly by the enzyme. Oligonucleotides have an extremely low efficiency as acceptor molecules. The attachment of oligoribonucleotides to the 3' end of RNA molecules by poly(A) polymerase is not known. It is not possible to attach

the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 2.4.02

By: _____
Bret E. Field
Registration No. 37,620

Enclosure

- Sarkar et al., *Biochem. Mol. Biol. Int.* (1997) 41(5):1045-50.

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